Imaging of Coronary Arteries Aid in Prevention of Atherosclerosis and Clinical Coronary Heart Disease

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Abstract: Prevention of progression of atherosclerosis is the best approach to reduce incidence of myocardial infarction, sudden coronary heart disease (CHD) death, stroke and peripheral vascular disease. Research over the past 40 years has identified the risk factors for atherosclerotic disease, noninvasive methods for measuring the extent of atherosclerosis in multiple vascular beds and very efficacious therapy to reduce the level of risk factors and prevent cardiovascular diseases. Cardiovascular incidence and death rates have declined. Nevertheless, rates of CHD and other vascular disease remain much higher in many countries and within select regions of certain countries than necessary. Prevention of atherosclerosis depends on 4 key steps: 1) a much more aggressive effort to lower modifiable risk factors, especially apolipoprotein-B (ApoB)-containing lipoproteins, low density lipoprotein (LDL) particles, LDL cholesterol, blood pressure, obesity, and smoking during adolescence and young adult years; 2) identify and treat elevated ApoB lipoproteins, diabetes and smoking cessation of very high risk young adults as early as possible; 3) use of imaging to identify atherosclerosis of coronary and other arteries for appropriate segments of the adult population and treatment of risk factors for those with identifiable atherosclerosis; and 4) improved approaches to deliver prevention of cardiovascular disease to large numbers of asymptomatic individuals identified by non invasive imaging to maximize adherence to therapies. The major missing piece is better methods to identify vulnerable coronary plaques on the verge of an atherothrombotic transition and better treatments to prevent "acute" events. However, the four steps above will still lead to very substantial reductions in CHD incidence and mortality.

Keywords: Coronary artery calcium, prevention, screening.

1. INTRODUCTION

We believe that the prevention of atherosclerosis is the goal for the reduction of incidence of most clinical coronary heart disease (CHD), myocardial infarction (MI) and angina and deaths due to CHD as well as other cardiovascular events [1, 2]. The task at hand is to improve the primary prevention of atherosclerosis; delay its progression and prevent atherothrombosis. The paradigm has now shifted to identifying and preventing heart attack over the lifetime of an individual [3]. Most current short term, i.e. 10 years, risk scoring systems identify only a relatively small percentage of all future heart attack victims as "at risk" candidates for lipid lowering therapy [4, 5].

Advances in epidemiology, clinical and animal experimental studies have documented the determinants of the risk of atherosclerosis and CHD across many populations. Levels of apolipoprotein B (ApoB) lipoproteins, blood pressure (BP), smoking, high density lipoprotein (HDL), ApoA$_1$, obesity, diabetes and physical inactivity are the primary determinants of the risk of CHD [6]. Modification of these risk factors decreased the risk of CHD in clinical trials or in large observational studies [7-9].

The CHD and cardiovascular disease (CVD) incidence and death rates dramatically declined in the United States and other countries but remain much higher in the United States compared to Japan, France and Italy [10, 11]. Countries with lower rates of CHD mortality and incidence have less prevalence of coronary atherosclerosis [12, 13]. The same risk factors are determinants of CHD among countries [14, 15]. In countries with low CHD rates in spite of similar levels of traditional risk factors or in countries with higher rates, there are likely unique lifestyle factors that are protective against atherosclerotic disease.

2. IS CHD PREVENTABLE?

Epidemiological studies have identified individuals who are at extremely low lifetime risk of CHD [6, 16]. Unfortunately, very few individuals, perhaps <10% of the population, meet low risk criteria, i.e. low blood cholesterol, BP, nonsmoking, no diabetes. Furthermore, the percentage of the population at low risk based on these criteria is not increasing over time [17-19]. The majority of the adult United States population and in many other countries have extensive atherosclerosis beginning at an early age such that by 60-65+ the majority of men and most women have extensive atherosclerotic disease as measured *in vivo* by various markers of subclinical atherosclerosis, i.e. coronary calcium, carotid intima media thickness (IMT), decreased ankle-brachial BP, or at postmortem examination. The development of atherosclerosis is not "normal" aging [20-24].

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The total atherosclerotic burden is the primary determinant of incident clinical CHD [16, 25]. MI, angina and sudden CHD death represent end-stage coronary atherosclerosis characterized by changes in plaque morphology and thrombosis [26, 27]. The incubation period for development of atherosclerosis begins in childhood, progresses over time and is determined primarily by levels of ApoB lipoproteins in the setting of other risk factors that increase endothelial vulnerability to lipoproteins and secondary inflammatory changes [16, 28-30].

Key risk factors, such as total and low density lipoprotein cholesterol (LDL-C) and BP, are "normally distributed" in the population and risk of disease is a linear function of risk factor levels from total serum cholesterol 150-160 mg% or systolic BP (SBP) $\geq$120 mmHg [31]. A high percentage of the adult United States population are candidates for pharmacological or lifestyle modifications to lower risk factor levels. There are estimated to be over 35 million with LDL-C >130 mg%, 70 million with BP $\geq$140/90 mmHg in the US adult population and even higher numbers are candidates for therapy if we accept "high" levels to be defined as LDL-C $\geq$100 and SBP $\geq$120 mmHg [30]. Most of the heart attacks occur among individuals with "average" level of risk factors, not very high levels because of the much higher percentage of individuals that are classified as intermediate or low risk factor levels. The absolute risk for an individual is directly related to level of their risk factors. For example, the Framingham Heart Study reported that 35% of heart attacks occurred among individuals with serum cholesterol $\leq$200 mg% [31]. Similarly, in the Multiple Risk Factor Intervention Trial (MRFIT) of nondiabetic men age 35-39 at baseline and 16 years of follow up, 24% of subsequent CHD deaths occurred among men with serum cholesterol $\leq$200 mg% and 60% with serum cholesterol $\leq$240 mg%, the latter 2 groups representing 77% of the MRFIT study population [32].

Populations with a low prevalence of atherosclerosis have very low CHD incidence and mortality. Individuals with very low coronary calcium scores, a marker of a low atherosclerotic burden have extremely low subsequent risk of clinical CHD [33-35].

Individuals with extensive coronary atherosclerosis may survive years without incident heart attack. Changes in plaque morphology induced by inflammation, and other factors leading increased vulnerability and risk of thrombogenesis and, in part, determine the immediate risk of incident CHD given the extent of atherosclerosis. The incubation period of conversion of atherosclerosis to clinical events can be very short - instantaneous sudden CHD death in asymptomatic individuals due to plaque erosion, rupture, thrombosis, and intra-plaque hemorrhage is well described [36, 37]. Importantly, the short term prediction of the risk of a heart attack in any individual, the exact time of plaque rupture, erosion or thrombosis cannot be measured in the population. Pathology studies show that rupture and erosion of plaques without clinical events may be very common [38]. Indeed, the amount of coronary atherosclerosis provides an excellent estimate of the population risk of developing clinical CHD but does not tell when any single individual within the population will have a heart attack or under what

circumstances this is likely to occur, such as during exercise, work, eating, stressful life events, etc.

Some investigators have wrongly concluded that without a better understanding of arterial biology, aggressive preventive approaches have limited benefit. They incorrectly postulate that if we could better discriminate individuals by the characteristics of atherosclerotic plaque, thrombogenesis, or fibrinolysis, then a smaller number of these individuals might require intensive pharmacological therapies to prevent thrombosis and heart attack.

This situation is analogous to the development of the polio vaccine. Only 1/1, 000 individuals infected with polio virus developed paralytic disease [39]. For many years prior to the Salk vaccine trials, major research efforts were directed at an attempt to identify the specific characteristics of individuals infected with the virus that would develop paralytic disease thus allowing the restriction of vaccine to a small subsample; perhaps 1/1, 000 infected individuals. The effective preventive approach with the Salk vaccine required vaccination of the entire population. The number needed to vaccinate to prevent one case was very high and adverse effects of the vaccine occurred given the large number of individuals vaccinated, especially early in the vaccine use [40]. Many argued then that without identifying the specific determinants of the tissue response to the virus, i.e. virulence, a vaccine was not feasible. This was clearly a wrong concept. Similarly, prevention of atherosclerotic disease has to be the key to substantially reducing the risk of clinical CHD. While we do not yet have a vaccine to prevent atherosclerosis, it is clear that very low levels of key risk factors in a population results in minimal prevalence of atherosclerosis and a low incidence of clinical CHD.

Therapeutic interventions at the time of a heart attack or secondary prevention after a heart attack have been effective in reducing morbidity and mortality [41, 42]. The majority of heart attack deaths still occur outside of the hospital and probably close to 20% of first heart attacks, especially in men, are sudden unexpected deaths. The current therapies for secondary prevention after heart attack substantially reduce risk of recurrent CHD and death in those to whom they can be applied [43-45]. The risk of CHD remains substantially higher than for primary prevention of incident clinical CHD and much higher than for those individuals classified as low risk of CHD. Acute treatments and secondary prevention are effective but will not solve the huge disability and costs of CVD. Primary prevention of atherosclerosis and its progression is the key to reducing CHD incidence and mortality and would have a major impact on health care costs for CVD, currently the most costly component of health care [46].

3. APPROACHES TO PREVENTING CVD

The key question now is how to implement a more effective primary prevention effort. There are at least 5 approaches to further reduce CVD incidence and mortality, two primarily for younger and three for older individuals. First, CHD is a common source epidemic due to adverse diet and lifestyle habits. We should apply a broad-based public health approach to prevent the increasing incidence with age and reduce the average level of risk factors and progression of atherosclerosis for the total population irrespective of

individual risk factor levels. The goal would be to modify the diet of the population so that average LDL-C or ApoB would be below 70 or 100 mg%, SBP <120 mmHg and also achieve tobacco cessation in a majority of the population, especially below the age of 40 or 50 [47]. Clinical CHD would then become a low incident and mortality disease and health care costs for treating CHD will likely decrease substantially. Unfortunately, we have only been partially successful in implementing a public health approach. For example, the 75th percentile for LDL-C for teenagers in the United States is over 100 mg%, i.e. 25% are at higher risk of atherosclerosis and 20% are cigarette smokers, assuring a continuing epidemic of CHD [48]. Improving "primordial prevention" of risk factors beginning in childhood by lifestyle-environmental modifications is an important goal which requires major changes in food processing, public health education and consumer behavior [49]. Primary prevention beginning in childhood or adolescence will have little impact on the current adult populations ages 50+ years that already have atherosclerotic disease and high risk of clinical CHD. Efficacious individualized preventive strategies must therefore remain a high priority.

Second, individualized nonpharmacological interventions may have their biggest impact at younger ages less than 40 in preventing the rise in risk factors with age and subsequent development and progression of atherosclerosis, i.e. primordial prevention. The extent of risk factor lowering, i.e. ApoB, LDL-C, may be less to prevent atherosclerosis or early progression than required to prevent heart attacks for individuals with more extensive atherosclerosis [50]. For example, it is possible to identify younger individuals with low short term but high lifetime risk [51]. An aggressive individualized primary prevention effort to lower risk factors to "ideal risk, " such as LDL-C <100 mg%, SBP <120 mmHg and especially smoking cessation, could have a major impact on lifetime risk. Such a nonpharmacological approach has been extremely difficult to implement for most of the population, especially less educated and lower socioeconomic status members.

There are three approaches for preventing heart attacks for individuals age 40 or 50+ who already have elevated risk factors and evolving atherosclerosis. First is the traditional risk assessment beginning usually for men at ages 40-50 and women age 50-60 and then implementing pharmacological and nonpharmacological therapies based on 10-year, risk score such as the Framingham risk score (FRS) as utilized by the current Adult Treatment Panel (ATP) III guidelines in the United States and similar guidelines in other countries [52]. This approach has shortcomings that can be improved by including longer term risk prediction beyond the traditional 10 years of current guidelines and/or including a wider list of CV outcomes as endpoints to increase the percent of population at high risk, i.e. 20% risk, of broader CHD diagnoses or cerebral vascular disease rather than hard "CHD events" or reducing the level of risk percent to institute pharmacological therapy, i.e. high risk redefined as 10 or 15% risk of heart attack at 10 years rather than the 20%. Unfortunately, most of these new methods still are likely to identify only 50-60% of potential heart attack victims as "at risk" requiring pharmacological therapies prior to heart attack. A large number of individuals destined to

have a heart attack will not be candidates prior to heart attack for effective pharmacological therapy.

The lifetime risk of clinical CHD is very high. A key report evaluated the distribution of 10-year and lifetime risk of CVD in US adults [53]. Only the traditional risk factors were evaluated, including SBP, total cholesterol, diabetes mellitus and cigarette smoking. If all risk factors were low, lifetime risk at age 50 for future CHD was only 5% for men and 8% for women. Only 8.4% of men and 14.3% of women are at ideal risk. If even 1 risk factor was not optimal, lifetime risk increased to 38% for men and 27% for women and if 1 risk factor was actually elevated, lifetime risk was almost 50% in men and 39% for women. Most important, 50% of individuals classified as low short term risk based on the FRS had a high lifetime risk of CHD. The important question, therefore, is whether we should implement the very efficacious lipid lowering and antihypertensive therapies for the majority of men and women with high *lifetime* risk irrespective of their *short term* risk rather than the present approach which focuses on individuals with high short term risk.

Fourth is measuring the extent and characteristics of subclinical atherosclerosis using computed tomography (CT) of the coronary arteries, carotid ultrasound or even possibly magnetic resonance imaging (MRI) of the coronary and carotid arteries [54, 55]. Treatment of risk factors would be based on extent of subclinical disease. Individuals with lower levels of risk factors but extensive atherosclerosis are probably "genetically susceptible" and would still have risk factors further reduced. Numerous epidemiological studies over the past 20 years have not identified any important new risk factors in the causal pathway for atherosclerosis and incident CHD. It remains possible that other undetected risk factors are primary determinants of atherosclerosis [56, 57]. Recently identified risk factors [58] either identify inflammation [59] in the atherosclerotic plaque or risk of thrombosis [60].

Fifth, provide a safe and cheap pharmacological preventive therapy for most adults, irrespective of their risk factor levels, beginning at younger ages, i.e. 30s-40s, to reduce the level of the key risk factors early in life and prevent or slow the progression of atherosclerosis to clinical CHD - the so called "polypill approach" for reducing CHD incidence and mortality [61]. Treating all adults who were not at low lifetime risk above would be at least equivalent to the polypill approach. This broad pharmacological approach should be the last resort or backup of our failure to successfully implement a population strategy to substantially reduce the levels of risk factors [10].

4. WHICH RISK ASSESSMENT METHOD IS BETTER?

The function of risk assessment is to segregate individuals into different risk stratums that provide guidelines for pharmacological and nonpharmacological therapies and for further diagnostic evaluations, i.e. exercise testing, nuclear and MRI imaging studies for the detection of myocardial ischemia, coronary angiography, etc. Risk assessment by itself cannot reduce the incidence of CHD. Actions, i.e. interventions, that are implemented following a risk assessment are the determinants of the reduction in risk

of CHD. There is no gold standard or scientifically proven risk assessment method or risk score to define good or bad risk assessment. No risk assessment method has been shown in randomized clinical trials to lead to a reduced incidence of CHD as compared to an alternate approach for the reason stated above. Therefore, a key question is which method or methods are most likely to identify the highest percentage of individuals at risk of a heart attack and, at the same time, successfully identify lower risk individuals who do not need pharmacological or even expensive nonpharmacological therapies.

The clinical "trigger" for the initiation of pharmacological therapy is determined by 4 factors: 1) the scientific evidence that a specific risk factor level is associated with the increased risk of a disease, i.e. CHD, CVD. Most risk factors such as ApoB lipoproteins and SBP, are linearly related to the risk of CHD across their usual distribution in the population [8, 62]. The risk factors are often normally distributed with little evidence of "bimodality, " etc. The differences in distribution of risk factors, i.e. BP, cholesterol, between those who do or do not get disease are small, with substantial overlap of levels of risk factors between the populations. Cutpoints are therefore arbitrary; 2) the evidence that a specific intervention such as lowering blood ApoB lipoproteins will reduce the incidence of CHD or CVD, and the consistency of such evidence across populations, race and sex groups [63]. Evidence that at a specific level of the risk factor or the magnitude of the change in risk factors by pharmacological, i.e. high versus low dose statins, etc., reducing SBP to ≤130 mmHg, or nonpharmacological intervention will be directly related to reduction of the incidence of CHD [64, 65]. Most clinical trials now suggest that at least a 30-40% reduction in LDL-C or ApoB may be required to demonstrate any significant reduction in the risk of clinical CHD [52, 66], especially among middle-aged and older individuals likely to have extensive underlying atherosclerosis. This has major implications because the nonpharmacological approach rarely can reduce LDL-C or ApoB by this magnitude over the long term for most participants in a program. Controversy continues as to whether lowering SBP below 130 mmHg, further reduces risk of stroke and renal disease, especially CHD, or whether treatment of diabetes will reduce risk of CHD.

3) The cost of the technology for the risk assessment, such as measurement of LDL-C, ApoB or LDL particles (LDL-P), oxidized LDL, BP or 24-hour BP or central BP measurement or measurement of coronary calcium or carotid ultrasound, etc. measured both as costs of measurement and potential follow up testing effects, exposure to expensive diagnostic tests [67]. A large number of individuals need to be screened in order to identify the relatively few who will develop incident CHD at least over the short term. Any screening technology must be relatively low cost and safe when applied to large numbers of individuals. This will usually require technology that is automated, can be administered by technicians and also include automated computerized readings that can be done by well-trained technicians. Screening is not a diagnostic procedure. Measuring ApoB or coronary calcium is not very useful in defining heart attack versus no heart attack in a patient presenting with severe chest pain to rule out MI [67].

4) The costs of the specific interventions, given that screening identifies an individual at risk, are of two types: a) monetary cost of the specific intervention, i.e. the cost of lipid lowering drugs, antihypertensive therapy, nonpharmacological therapies to reduce risk factors; and b) the cost of adverse events associated with the specific intervention, i.e. adverse effects of antihypertensive therapy, lipid lowering statin therapy [68, 69] as well as nonpharmacological therapies such as injuries associated with exercise, sudden death during an exercise program, depression and suicide following weight loss programs, etc. [70].

The decision level, i.e. the FRS or level of coronary calcium, carotid IMT, etc., that results in pharmacological versus nonpharmacological therapies is based on the above 4 factors. The decision level for treatment will change with results of new trials or other clinical research, i.e. identification of genetic host susceptibility. Clinical trials documenting the benefits of treating BP have changed guideline levels to begin antihypertensive drug therapy to lower initial BP levels [71]. This resulted in an increasing number of candidates for pharmacological therapy to lower their BP. The level of risk factors, such as BP, LDL-C, ApoB, are usually near normally distributed in the population. Therefore, there is a substantial increase in the number of individuals eligible for pharmacological therapy as the level of recommended therapy begins to move toward the mean or median of the population. A key element in this decision process is the comparative benefits of the pharmacological or surgical therapy versus nonpharmacological therapies to reduce the level of the risk factors and the incidence of clinical disease. Individualized preventive nonpharmacological therapies for lowering BP, LDL-C, reduction of body weight and even exercise are relatively ineffective in middle age and older individuals primarily because of lack of long term adherence to behavioral interventions and difficulties of individualized lifestyle modifications.

The cost of therapies, as noted, also becomes a key factor for determining the specific level to begin pharmacological therapy. The cost of lipid lowering drug therapies, such as statins, as well as BP therapies has declined dramatically over time. Pharmacological therapies are now relatively inexpensive and have a good long term safety track record although there are still adverse effects [72-75].

The decline in costs of drugs and long term safety and efficacy of drug therapy has changed the goals of risk assessment. High sensitivity, i.e. the ability of a risk assessment method to identify a very high percentage of individuals likely to develop a heart attack over long term, is of greater priority than specificity, misclassification as high risk. The polypill is an extreme example of pharmacological therapy for everyone irrespective of risk score and therefore "increases sensitivity" to close to 100% [61].

There is a strong positive association between risk scores such as the FRS and subsequent CHD events [76]. The c-statistic, a combination of sensitivity, i.e. to predict CHD, and specificity to predict no CHD, is often used as a measure of quality of a risk assessment method. The c statistic can be deceptive; a high c statistic can still result in many at-risk individuals, i.e. likely to have a heart attack and classified as

not candidates for drug therapy [77]. The risk of CHD is continuous across range of risk factor levels. Arbitrary classification into 10 year low, intermediate and high risk to determine pharmacological therapies, results in many individuals who subsequently have a heart attack being initially classified as either low or intermediate risk and therefore not recommended for pharmacological therapies. Such individuals represent a failure of preventive therapies, especially among women [17, 78].

The short term risk prediction models led to a misconception that younger individuals and women, unless they have diabetes, are not at high risk of CHD [76, 77]. The higher risk candidates for pharmacological therapies consisted predominantly of older men and women with diabetes. A recent paper from the National Health and Nutrition Examination Survey (NHANES) 1999-2004 evaluation showed that no women age 35-44 years met the Framingham criteria of high risk, (>20% risk in 10 years) and only 0.6% of women aged 45-54 years were high risk. The majority of women who have a first heart attack do not meet the criteria for being high risk or even intermediate risk based on the FRS [79].

A recent evaluation for risk scoring methods, such as the FRS, for CHD noted that the few randomized trials of risk scores and subsequent modification of risk factors showed no benefit on intermediate CHD outcomes. Furthermore, there is strong evidence that physicians do not use the risk scores [80, 81]. Similar results have been noted in other countries. Another important question is whether knowledge of a "high risk" status actually changed behavior of those patients. The authors concluded that risk scoring was not necessarily associated with increased awareness or behavior changes [82-87].

5. IMAGING OF ATHEROSCLEROSIS

The extent of atherosclerosis is the most powerful determinant of the risk of clinical CHD based initially on studies of patients with suspected angina who had coronary angiography before the development and wide application of coronary bypass surgery [88]. Subsequently, peripheral measures of subclinical atherosclerosis, such as ankle-brachial index [89, 90], carotid imaging [91], and CT to measure coronary calcium, were shown to be powerful predictors of the risk of CHD as was a composite measure of subclinical disease [92]. Quantification of the extent of coronary artery calcium has been documented to be a powerful predictor of the risk of clinical CHD independent of traditional risk factors [93-96]. A recent report from the American College of Cardiology and the American Heart Association supported computed tomography (CT) to measure coronary calcium as "reasonable" for asymptomatic adults at intermediate 10-20% 10-year risk and at low to intermediate 6-10% risk but not for individuals with low <6% risk [97]. The extent of coronary calcium is a strong and independent predictor of the risk of clinical CHD in men, women, middle-aged and very old, black, white, diabetic and nondiabetics. The association is continuous across levels of coronary calcium probably from a calcium score of 10 Agatston units or even less. Some investigators suggest that a coronary calcium score ≥100 may be high risk and ≥400 may be very high risk. Individuals with 0 coronary

calcium scores are at very low risk of clinical CHD events [98].

The key question is whether the use of imaging technologies will improve prediction of CHD so that the majority of individuals likely or not likely to have a heart attack are correctly identified. Does imaging of coronary arteries and other subclinical evaluation, i.e. carotid IMT, provide better information on deciding what individuals need more aggressive therapy than traditional risk scores? [99].

The imaging of coronary arteries, i.e. measurement of coronary calcium, is not widely accepted as a standard preventive medicine practice to identify individuals at risk of clinical CHD events. An argument of many naysayers is that measurement of coronary calcium has not been proven in a clinical trial to reduce the incidence of CHD or CHD deaths and that the radiation dose might increase the risk of cancer and negate any benefits from the wide use of this technology. It has also been suggested that measurement of coronary calcium will lead to unnecessary further diagnostic and surgical procedures and therefore substantially increase health care costs [100, 101].

It is also suggested that individuals will have heart attacks with relatively little coronary atherosclerosis whether measured indirectly by coronary calcium, i.e. 0 coronary calcium score, or by the extent of coronary stenosis as measured by angiography or at postmortem examination. Such individuals are rare in the population. The pathogenesis of heart attacks among such individuals may be due to coronary artery spasm, rupture of an isolated coronary plaque or possibly due to unexpected stressors, such as tachycardia, vasovagal response, extensive bleeding. It is also possible that there is a small population which has only noncalcified atherosclerotic plaques and still has a significant atherosclerosis burden in spite of a low coronary calcium score. However, the number of such individuals must be very low given the extremely low risk of CHD, at least over 5-6 years, among individuals with 0 coronary calcium scores [102].

Newer diagnostic techniques using multiple-detector computed tomography (MDCT) [103, 104], especially with contrast agents can identify both noncalcified and calcified plaques. This has led to proposal that these new methods are superior than to just measuring coronary calcium as a screening technique. However, there is no evidence that MDCT, measurement of both calcified and noncalcified plaques, among normal asymptomatic individuals improved risk prediction above measurement of only coronary calcium. There is no consistent evidence that noncalcified plaques are associated with higher risk of clinical CHD than calcified plaques. It is likely that almost all individuals who have multiple noncalcified plaques have calcified plaques as well and will have high calcium scores.

Traditional risk factors that are part of risk assessment are strongly related to the development of atherosclerosis and to the extent of coronary calcium [28, 105]. The association is not 1:1 however. If there was a perfect 1:1 relationship between risk factors such as LDL-C and extent of atherosclerosis then measures of coronary atherosclerosis, i.e. coronary calcium, would be unnecessary. The reason why there is not a 1:1 relationship between risk factors and

extent of coronary calcium are first, substantial within-individual variation over time in risk factor levels. A single measurement of a risk factor is not the same as true mean, median for an individual over time, even in the short term. The incubation period is very long for the development of atherosclerosis and subsequent risk of clinical CHD and therefore the levels of risk factors measured early in life and the changes in these risk factors over time contribute to the progression of atherosclerosis. A lipid level measured several years before a coronary calcium study may miss the lifetime risk exposure. A recent long term 30-40 year follow up from a Chicago cohort documented a strong positive association between risk factor levels at younger ages and extent of coronary calcium 30-40 years later [2]. Similarly, genetic studies demonstrate substantial increased risk of both CHD and extent of atherosclerosis in individuals with elevated childhood blood LDL due to specific genetic polymorphisms [106].

Short term, 10-year, risk scores determined at time of coronary calcium measurement results in substantial misclassification of the extent of coronary atherosclerosis especially among women and younger age groups [107, 108]. For example, in a study involving 2, 447 nondiabetic asymptomatic women, mean age 55 ±10 years, 90% of the women were classified as low risk, 10% as intermediate risk and none as being high risk, i.e. >20% risk of clinical CHD in 10 years. Coronary calcium, however, was present in 33% of the women and 13% had coronary calcium >100 which is associated with a high risk of CHD. 20% had age- and gender-adjusted coronary calcium scores >75th percentile and 84% of these women were classified as low risk.

The Multi-Ethnic Study of Atherosclerosis (MESA) study reported that for coronary calcium measurement among both men and women, the risk of heart attack by level of coronary calcium was independent of the FRS, at least within the intermediate risk level of FRS, for the majority of the participants. They further identified the disconnect between recommendations for lipid lowering therapy based on ATP III guidelines and coronary calcium measurements at baseline. For example, among 663 participants with coronary calcium score >400, clearly at very high risk of clinical CHD, only ½ met current ATP III criteria for lipid lowering therapy. On the other hand, among 3, 361 with 0 coronary calcium scores and at a very low risk for clinical CHD events, 674 (approximately 20%) were candidates for lipid lowering therapy based on ATP III guidelines [109]. The amount of coronary calcium is a measure of atherosclerosis. It should not be primarily used as a method to reclassify individuals based on a Framingham or similar risk score. Atherosclerosis, not a risk score or lipid level, is the determinant of likelihood of clinical CHD.

Measurement of coronary calcium does not provide a good technique for determining progression of coronary atherosclerosis. There is little evidence at the present time that lipid lowering therapies modify the progression of coronary calcium scores [110-114]. Most of these studies evaluating lipid lowering have involved populations with high coronary calcium scores. It is possible that coronary calcium measurements may still be useful for evaluating progression from 0 or very low coronary calcium over time [115].

There is little evidence that measurement of coronary calcium results in substantial increase in further invasive diagnostic tests. Individuals with very high coronary calcium scores have an increased likelihood of further invasive diagnostic tests [67, 116]. In populations with very low incidence and mortality due to CHD, the prevalence of atherosclerosis will be low and therefore a much lower percentage of the population will be identified as having any coronary calcium or coronary occlusion. In such populations, the value of imaging to identify high risk individuals for preventive therapies and reduction of CHD may not be cost effective [117].

The radiation dose from coronary CT has been implicated as a reason for not recommending screening for coronary calcium or noncalcified d plaque. A Scientific Advisor from the American Heart Association noted that the effective dose for coronary calcium scan was 3 msv to 9 msv using a 64-slice coronary CT, with modifications [103]. They noted that it is extremely difficult to estimate risk, morbidity or mortality at these low radiation doses. Average background radiation in the United States is between 1-10 msv. They noted that the population lifetime risk of developing a malignancy is about 41% and dying of malignancy is about 21%. Compared with the lifetime risk, coronary CT angiography with a 10 msv dose increases the risk of cancer by 0.05%. Arguably a trivial effect but one that could be important at the population level with many thousands of tests being performed [118-120]. A recent report from the Radiological Society of North America estimated that the average lifetime risk of developing radiation-induced cancer (mostly lung cancer) following a cardiac CT is 0.12% [121]. No study has actually measured the risk of developing either cancer in general or site-specific cancer following CT or similar procedures or at similar dose of radiation [122]. Such a study would require an extremely large sample size and is probably not feasible. Furthermore, another recent study documented that prospective gating of multidetector CT (MDCT) test would substantially reduce the exposure dose [123, 124]. Widespread use of coronary CT will require continued careful monitoring of radiation exposure and efforts to minimize dose. There is little indication for frequent repeat coronary calcium studies [125].

Risk assessment either by scores such as the FRS or measurement of subclinical vascular disease such as coronary calcium scores will not reduce the incidence of CHD in and of themselves. Individuals identified for specific pharmacological or even nonpharmacological therapy must adhere to long term therapy with a reduction in the level of the risk factors. Poor adherence to therapies may be the single most important impediment to a major reduction in the incidence of CHD and CVD irrespective of the risk assessment method. The ability of various risk assessment methodologies to increase adherence to recommended therapies become an important component of the evaluation. For example, will individuals identified as having a higher coronary calcium score adhere to long term pharmacological therapies better than similar individuals identified as intermediate or high risk by an elevated FRS? [116, 126].

Recent studies have suggested improvement in adherence to therapies after CT scanning, especially for individuals with high coronary calcium [97, 116, 125, 126].

Measurement of carotid IMT and plaque by ultrasound is correlated with the extent of coronary atherosclerosis and coronary calcium, as well as with levels of traditional risk factors, (especially BP, lipoproteins, and the presence of diabetes) [127-129]. Intervention studies have generally shown that reduction of risk factors, such as BP or LDL-C or increased HDL-C, results in regression or slowing of progression of IMT [130, 131]. Regression or slowing of progression of carotid IMT has been correlated with reduced incidence of CHD [132-133]. Recent studies have measured the type of plaque in the carotid artery using MRI or ultrasound and reported differential risk of both stroke and CHD by characteristics of plaque [134]. Carotid ultrasound or MRI has been proposed as a method of identifying "vulnerable plaques." [135, 136] MRI may also be a future method to measure extent of coronary artery disease [137, 138]. Carotid IMT has been proposed as an alternative to coronary calcium because of lower cost, no radiation exposure and better quantitative screening. There may be an important role of carotid IMT in evaluating younger individuals. Also at present it may be the only population measurement of progression or regression of disease in primary prevention, i.e. patients without prior CHD, CVD. The basic problem with the use of IMT is that it is a composite measure of both intima and media changes in the vessel and is therefore affected by vascular remodeling in response to atherosclerosis. In addition it remains very technician dependant for quality and reproducibility [139, 140].

Intravascular ultrasound (IVUS) is an invasive approach that has been used very successfully to measure changes in atherosclerosis within the coronary arteries in relationship to various interventions, including the effects of both HDL-C and LDL-C primarily in individuals with preexisting CVD [141-143]. IVUS has been used in a series of clinical trials to document the benefits of more aggressive therapies to modulate regression of atherosclerosis [144, 145]. There is a good correlation between changes in plaque and reduction in the incidence of CHD. IVUS is an invasive technique limited usually to individuals who have clinical CHD and has provided the best evidence to date of effects of interventions to modify plaque progression [146].

6. RISK FACTOR REDUCTION AND CHD INCIDENCE

There are no clinical trials demonstrating that lowering the LDLC, ApoB, LDL-P among individuals who have high coronary calcium scores but intermediate or low FRS or other risk scores results in a reduction in clinical CHD events [147]. Invasive and noninvasive techniques, i.e. angiography, IVUS, carotid ultrasound, have documented that lipid lowering or other risk factor modification results in a decrease in the extent of atherosclerosis. Reduction in risk of CHD is noted across the entire level of LDL-C. This strongly suggests that lipid lowering among individuals with significant atherosclerosis, i.e. high coronary calcium score, will result in decreased risk of clinical CHD.

There is no clinical trial evidence that use of FRS or other risk scores results in a decreased incidence of or

mortality due to clinical CHD. A "screening test" does not by itself reduce incidence of disease. The therapeutic decisions based on screening tests and how successful they are applied determine the benefit of a screening test. A proposal for a trial to determine whether measurement of coronary calcium reduces risk of CHD will be very expensive, over a long time period and will likely demonstrate that more at-risk individuals on statin therapy have a lower risk of CHD.

7. PROPOSED RECOMMENDATIONS

We believe that any risk assessment method should identify at least 80% of individuals likely to have a heart attack over 30-40 years. None of the current risk assessment methods except measurements of coronary calcium or abandoning risk assessment and treating practically everyone or greater than low long term risk, or the polypill approach, can reach this goal. There is relatively little difference between treating the 75% of the population over age 20, i.e. 117 million, who have higher lifetime risk versus the polypill [66].

Psaty, *et al.*, [148-151] have suggested that treating most adults except for very low risk was cheaper than coronary calcium screening. The costs of coronary calcium screening are determined by cost of test, including interpretation, and need for repeat screening over time. A possible design (Figs. **1**, **2**) shows that coronary calcium screening is probably equal or less costly than treating everyone over 40 or 50 years of age with lipid lowering therapy. The key cost variables are cost of CT screening; frequency of CT examination; costs of drug(s) and cost of physician visits. The advantage of coronary calcium screening is that higher at-risk individuals can be identified. The preventive therapies can be stratified by the extent of coronary calcium. There is a small percentage of older women with 0 coronary calcium who do not need lipid lowering drug therapy.

The proposed model suggests that repeat coronary calcium studies are probably unnecessary for most individuals once presence of coronary calcium is detected, at least ≥10 Agatston units, because regression of coronary calcium scores is rare and progression is poorly correlated with "treatment effect, " i.e. lipid lowering. For individuals with 0 coronary calcium, repeat scan every 10 years is probably adequate given an average of conversion from 0 to any calcium of about 6%/year, at least for older men and women. Studies show that risk of CHD is very low for 0 coronary calcium, at least over the next 5-6 years.

The model assumes that: 1) very high risk individuals will be provided preventive pharmacological therapies without prior coronary calcium measures, including men and women over 40 years of age with type 1, 2 diabetes, strong family history of premature CHD, very high ApoB, LDL-C levels and/or cigarette smokers. This model substantially reduces radiation exposure and costs of screening. We estimate a cost of $200 per scan. For a cohort of 1000 women as shown in Fig. (**1**) there would be approximately 2, 000 scans over 30 years at a cost of about $400, 000. For men (Fig. **2**), from age 45-70+, there would also be about 2, 000 scans at accost of $400, 000. An increase in frequency of scans to every 5 years would not double cost because individuals with new coronary calcium would not need repeat scans.
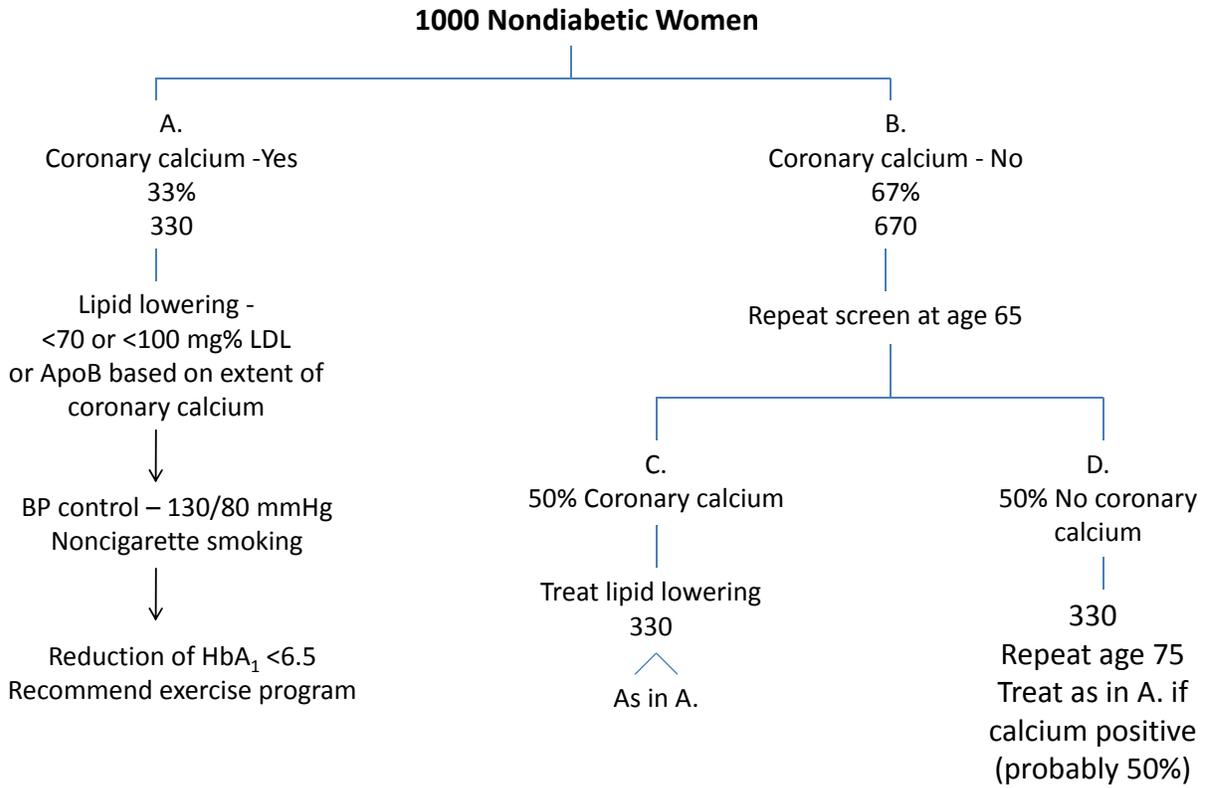
1000 Nondiabetic Women

A.
Coronary calcium -Yes
33%
330

B.
Coronary calcium - No
67%
670

Lipid lowering -
<70 or <100 mg% LDL
or ApoB based on extent of
coronary calcium

Repeat screen at age 65

C.
50% Coronary calcium

D.
50% No coronary
calcium

BP control – 130/80 mmHg
Noncigarette smoking

Treat lipid lowering
330

330
Repeat age 75
Treat as in A. if
calcium positive
(probably 50%)

Reduction of HbA_1 <6.5
Recommend exercise program

As in A.

Fig. (1). Age 55 begin screening - women.

1000 Nondiabetic Men

A.
Coronary Calcium - Yes
50%
500

Coronary Calcium - No
50%
500

Lipid lowering –
<70 or 100 based on extent of
coronary calcium

Repeat Screen at Age 50

B.
Coronary Calcium – Yes
25% (125)

C.
Coronary Calcium – No
375

BP control – 130/80 mmHg
Noncigarette smoking

Treat lipid lowering

Repeat age 60
Treat as in A. if
calcium positive
(probably 50%)

Reduction of HbA_1 <6.5
Recommend exercise program
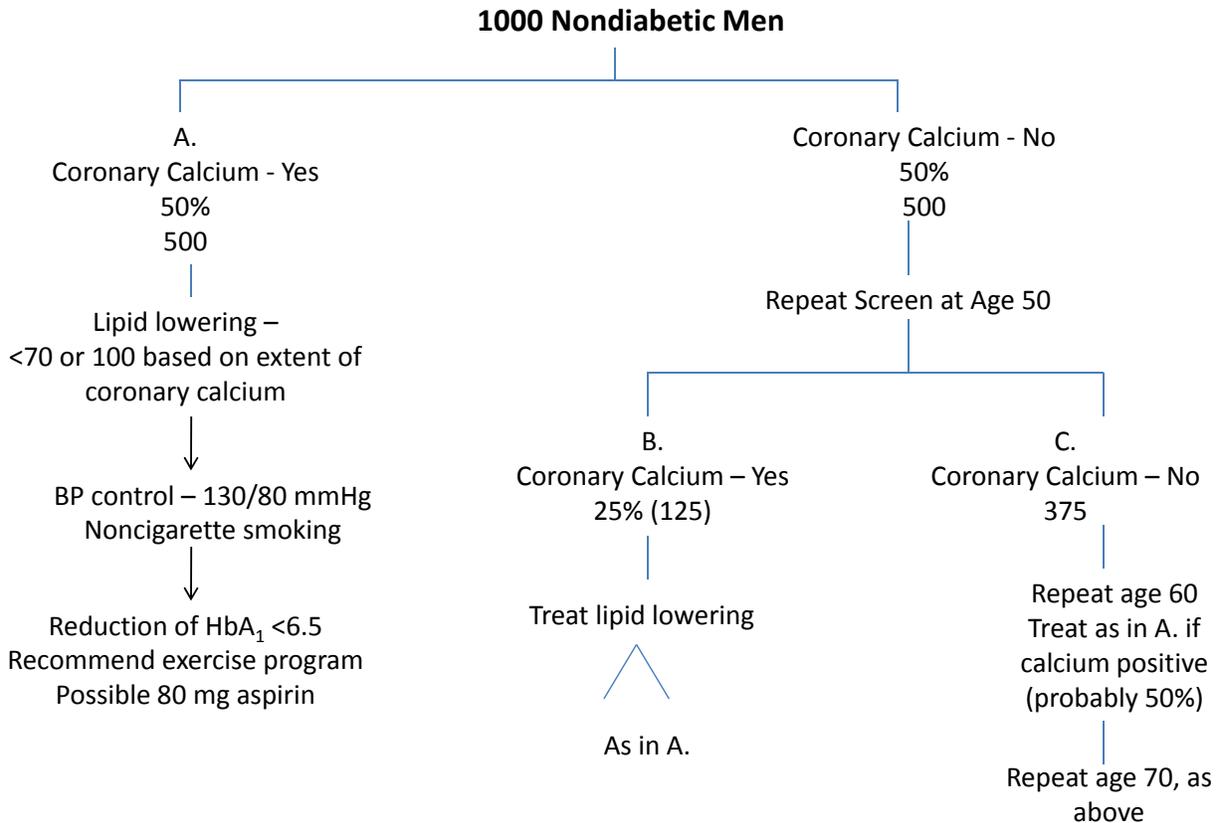Possible 80 mg aspirin

As in A.

Repeat age 70, as
above

Fig. (2). Age 45 begin screening - men.

The cost of lipid lowering therapy is estimated at about $80-100/per year (generic). For women (Fig. **1**), 330 women age 55-64 would be treated, 670 age 65-74 and 850 age 75-84 excluding deaths and dropouts, at a total cost of $1, 482, 100. If all women age 55+ were put on lipid lowering drug therapy the cost would be $2, 400, 000 over 30 years. Therefore, for women the costs of screening and selective lipid lowering drug therapy is a little lower than treating all women at age 55. Similarly, for men cost of drug therapy age 45-80+ would be about $2, 300, 000. The cost of lipid lowering therapy may be too low because a percentage of individuals will require more potent lipid lowering drugs that are not "generic." However, the cost would likely be similar for any method of risk assessment. The costs of other drug therapy to lower BP, etc. would probably not be different by method of risk categorization since everybody with BP ≥130 to 140 mmHg based on current guidelines would be treated. Aspirin is very inexpensive and would not contribute much to overall costs. There is still controversy about aspirin's risks-benefits in primary prevention. Important unanswered questions are whether individuals with impaired fasting glucose or glycohemoglobin >6.0-6.5 but not diabetic should be placed on glucophage and/or nonpharmacological therapy or other glucose lowering drugs and how to treat individuals with low HDL-C and elevated triglycerides. Clinical trials using HDL-C as a target of therapy have been disappointing but newer, more potent drugs may change the risk-benefit ratio [152].

We estimate that the 10-year incidence of CHD was 5% among women age 55-64, 10% age 65-74 and 20% age 75-84, i.e. 315 events between age 55-84 per 1, 000 women. Ninety percent will occur among women with some coronary calcium (n=283). If preventive therapy is 80% successful, then the reduction in risk of CHD event will be 225 or 68% and if 80% occur among women with coronary calcium (n=252) and 80% prevented 201, or about 2/3 of CHD events can be prevented at relatively low cost. The estimates are similar for men (see Appendix Table). Assume 550 CHD events age 45-84, 90% had coronary calcium, 80% effective in reducing CHD or 396 events.

The major limiting variable will be the need to maximize long term adherence. A simplified screening program and preventive therapy with much greater emphasis on long term adherence will greatly improve a preventive program. The current approaches of complex risk assessment and tailored therapies, costly follow up physicians visits likely results in poor adherence to preventive therapies by focusing on diagnostic testing and complex guidelines and more expensive drug therapy.

8. DISCUSSION

CHD is preventable. We need better strategies to maximize the percentage of at-risk populations receiving optimal preventive therapy(ies), both pharmacological and nonpharmacological.

The proposed preventive strategy has 3 pieces. First, for children and young adults there should be a much greater efforts to prevent cigarette smoking, the rise in risk factors, BP, ApoB lipoproteins, blood glucose, weight, and increase physical activity. If we do not modify risk factors in young adults now, then we are doomed to a continued endemic of CVD [153-155]. This should remain a very high priority. Second, for very high risk young adults <45 for men, 55 for women, as previously defined, apply pharmacological or nonpharmacological individualized primary prevention of elevated risk factors. Third, at age 45 for men and 55 for women, begin CT screening for coronary calcium. Everyone with coronary calcium either ≥0 or >10 requires pharmacological-based risk factor reduction to slow or prevent progression of atherosclerosis and incident clinical CHD. Repeat coronary calcium at periodic intervals, approximately every 10 years only for those with 0 or <10 coronary calcium scores to age 75-80. The intensity of lipid lowering therapy, BP reduction, other therapies, would be individualized by physicians and based on initial coronary calcium score and level of risk factor(s).

Fitness as measured by maximal exercise testing could provide an important adjustment to risk stratification based on imaging. How such information would be used needs further evaluation [156]. A clinical trial to evaluate the role of "fitness, " as opposed to ischemic changes, as measured by exercise testing in combination with coronary calcium measurements and aggressive pharmacological and non therapies, such as exercise, could provide important new information. A basic problem could be implementation of maximal exercise testing, standardization, costs and willingness of individuals to complete these tests. Similarly, any new pharmacological therapies will require clinical trials. The Psaty recommendation to place practically all adults on lipid lowering therapy could be a viable alternative in populations that lack cost-effective imaging facilities.

New research should focus on better risk markers that would enhance short term prediction of a heart attack, including thrombogenesis, unfavorable changes in plaque morphology, and platelet function. We are still unable to predict very short term risk of a heart attack. If, for example, could we monitor a blood marker of change in platelet function, risk of thrombosis, depressed fibrinolysis, or inflammation, in a plaque that is likely to rupture and could do so in a cost effective manner, it would be advantageous. Sadly, to date we have not been very successful [157, 158].

There is a need for better nonpharmacological and pharmacological therapies, i.e. exercise, omega-3 fatty acids, vitamin D, antiplatelet aggregating agents, clotting inhibitors, that can be demonstrated to reduce risk of thrombosis, rupture, fissure in plaque, etc., precipitants of heart attack, that are both safe and efficacious.

This approach does not preclude the development and replacement of CT for measurement of coronary calcium by new imaging technology, especially noninvasive, safe, low cost and low radiation approaches that can monitor effects of therapies on the extent of atherosclerosis and risk of CHD over time in primary prevention. Measurement of coronary calcium, as noted, does not provide a good approach for evaluation of effects of therapies and, therefore, once an individual has coronary calcium at least above 10 Agatston units, repeat calcium measurements, except in research, are of limited value. IVUS at present is the best approach for monitoring effects of therapy or progression of coronary atherosclerosis but is too invasive for application to the general population. MRI may be an approach for the future.

Standardization of new imaging techniques and readings should be a high priority.

We need improved systems approaches to delivering long term, lower cost preventive therapies for large numbers of asymptomatic individuals. Delivery of preventive services in physicians' offices will not be cost effective and will likely result in high rates of nonadherence to therapy and loss to follow up. Physicians are responsible for preventive therapies but require substantial ancillary support to maintain adherence and follow up for asymptomatic individuals.

Our prevention approaches must reach the lower socioeconomic and higher risk populations and decrease the substantial disparities in CVD. A simplified, lower cost approach is much more likely to be successful.

9. CONCLUSION

CHD is preventable. Incidence and death rates due to CHD and vascular disease are too high in many countries and within countries, there remains substantial disparity of CHD rates. A successful prevention program must focus on prevention of atherosclerosis beginning in childhood by lowering the multiple risk factors. Hopefully in the future, better genetic approaches will improve our ability to identify "susceptible" individuals and improve selection of specific drug therapies. That said, atherosclerosis is very prevalent in the population and it is extremely doubtful that we will identify a genetic footprint for "susceptibles" versus "nonsusceptibles."

The proposed preventive approach using imaging and simple, low cost and safe preventive therapies can substantially reduce CHD incidence and also stroke, greatly reduce costs of treatment of CHD and reduce population radiation exposure by decreasing incidence of CHD [159]. Finally, any screening program or risk assessment alone will have little effect on reducing CHD morbidity, mortality and disparities within and among populations. The key is correctly using the information to maximize prevention of atherosclerosis, thrombosis and clinical disease.

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CONFLICT OF INTEREST

None declared.

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